Langerhans'-Cell Histiocytosis in Adults

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Guided by a long-term retrospective observation, the clinical course and treatment of Langerhans'-cell histiocytosis (LCH) in adult patients are represented. The series included 19 patients meeting the histopathologic criteria of presumptive LCH who were followed for 1.5–20 years (average 7.7 years).

Most frequently, skeletal lesions (16 patients), diffuse interstitial lung infiltrates (seven patients), and pituitary gland involvement with diabetes insipidus (four patients) were present. Bone lesions of the skull and axial skeleton were associated with an infiltration of adjacent soft tissues in 10 of 16 patients. Liver, lymph node, and bone marrow involvement appeared sporadically.

LCH was divided into localized or multifocal form. Localized disease took a benign course with remission of bone (n = 4) or lymph node lesions (n = 2). Also, in isolated pulmonary LCH (n = 2), spontaneous transition to inactive disease occurred. With the exception of isolated bone lesions (n = 27), which remained asymptomatic or showed a remission to treatment, multifocal LCH had a more aggressive course. Osseous lesions with adjacent soft tissue infiltration (n = 20) showed a relapse rate in excess of 80% independent of the treatment applied. Pulmonary involvement led to a more marked functional impairment compared to the isolated form, and systemic treatment yielded no convincing effect. In three patients with liver or bone marrow involvement, LCH showed a persistent, serious disease activity. One patient died of transition into acute monomyelocytic leukemia 18 months after diagnosis without preceding chemotherapy.

In adults, LCH seems to be limited to a few organ systems. Multifocal LCH represents the more aggressive form with unfavorable prognosis in patients with bone lesions spreading into the adjacent soft tissue and liver or bone marrow involvement.

Key words: diabetes insipidus, eosinophilic granuloma, histiocytosis X, interstitial lung disease, soft tissue lesions

INTRODUCTION

The disease designed as Langerhans'-cell histiocytosis (LCH), formerly histiocytosis X, comprises a wide spectrum of clinical manifestations associated with a specific histopathologic lesion, the proliferation of Langerhans' cells (LC). These atypical but mature cells of the mononuclear phagocyte system can infiltrate virtually any site of the body and may occur as a localized lesion or as widespread systemic disease [1–3]. The clinical picture is heterogeneous, with skeletal, cutaneous, lymphoreticular (including liver, spleen, lymph nodes, and bone marrow), pulmonary, and pituitary gland involvement seem most often [4–10]. Infiltration of the reproductive organs, the central nervous system, the pituitary gland, or the gastrointestinal tract is described sporadically [11–14]. Although the etiology remains unknown, immune dysregulation has been suggested in the pathogenesis of this disease [3,15]. More recently, the detection of clonal histiocytes in different clinical forms of LCH seems to indicate a neoplastic disorder arising from mutations of bone marrow precursor cells [16].

A few studies have focused on the clinical features and treatment in adult patients. More than two thirds of cases are diagnosed in childhood and even in large series, children account for more than 90% of patients [5–7,17,18]. Therefore, more than 100 years after the first description of LCH by Alfred Hand, we would like to present our experience with 19 adult patients affected by LCH.

MATERIALS AND METHODS

We reviewed the charts of all patients aged 18 years or older in whom LCH was diagnosed in the Department of Internal Medicine and/or Radiooncology from 1970 through 1991. Criteria for inclusion in the series were documented follow-up of at least 12 months duration and thorough histology review to confirm diagnosis and organ involvement. According to Gramatovici and D'Angio [19], LCH was divided into localized and the multifocal forms. Localized disease was defined as LCH involving one soft tissue site, with or without one site of bone

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involvement. Isolated pulmonary involvement was included in this group. Multifocal disease was defined as involvement of two or more soft tissue sites, with or without bone involvement. Patients with involvement of multiple sites of the same system or multiple bone sites and a single soft tissue area were included in this group. Disease activity was established on clinical grounds. Active disease has been defined as 1) chronic progression (C), 2) new symptomatic, histologically verified organ manifestations (extension, E), or 3) local disease recurrence after initially successful therapy (R). Inactive disease was defined as 1) no lesion/disease (ND), 2) stable asymptomatic (SA), or 3) stable symptomatic but not progressive disease (SS). Treatment modalities were categorized as local (surgical excision, radiotherapy) or systemic (glucocorticoids, cytotoxic drugs) therapy. Response criteria were estimated according to disease activity. No response (NR), meaning progressive disease or no improvement of organ dysfunction, and local recurrence (R) against complete (no disease, CR) or partial (disease regression, PR) remission were differentiated.

The histology was carefully reevaluated in all cases. Basic to all lesions was an inflammatory process, as evidenced by the presence of granulation tissue and a mixed population of inflammatory cells including eosinophils and neutrophils with a tendency to form granulomas (Fig. 1). The hallmark of all lesions was the presence of LC, i.e., mononuclear cells that resemble histiocytes but differ from them by their acidophilic cytoplasm and indented, reinform, and often longitudinally grooved nuclei. The diagnosis of LCH was established when, in the presence of a characteristic morphology, the atypical histiocytic cells reacted with the antibody to S 100 protein (Dakopatts, dilution 1:2000) using the streptavidin-biotin-complex method. Biopsies of all organs affected, with the exception of the pituitary gland, were reviewed and fulfilled these requirements. The material was not suitable for the additional immunohistochemical reactions or for electron microscopy as recommended by the Histiocyte Society for a definitive diagnosis of LCH [3].

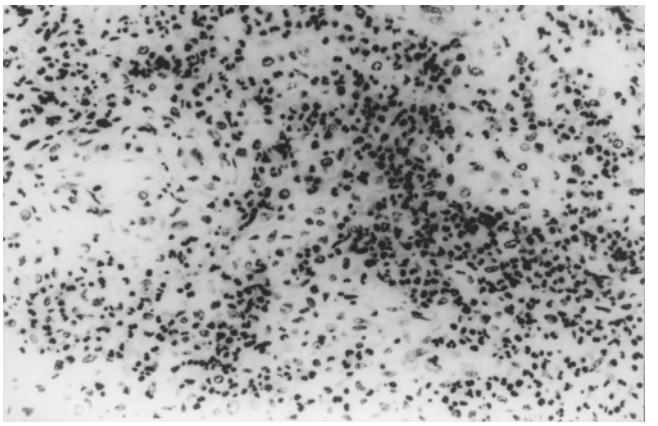

Fig. 1. LCH (eosinophilic granuloma) of the mandible in a 28-year-old man. Curettings reveal the typical morphology of an inflammatory infiltrate including eosinophils and a histiocyte-like mononuclear cell population that proved to express S 100 protein. (HE, ×250).

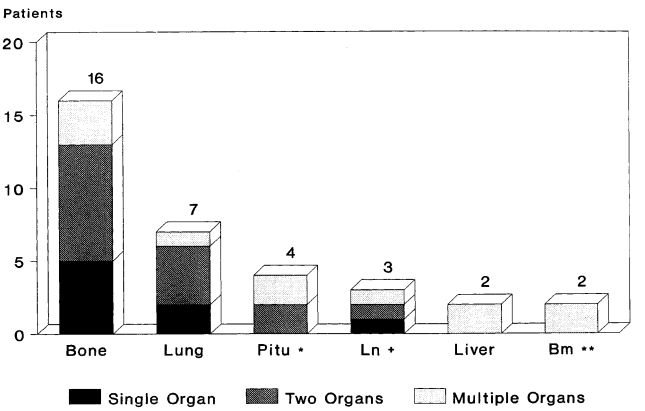

Fig. 2. Organ manifestations of LCH in the present series of 19 adult patients and the proportion of single, two organ, or multiorgan (>3 organs) involvement related to diseased organ systems.

RESULTS

Our series includes 19 adult patients (12 men, 7 females) ranging in age from 19 to 65 years (mean 37 years) at the time of diagnosis. Documented follow-up averaged 7.7 years (range 1.5–20). The sites and extent of disease in relation to organ systems affected by LCH are shown in Figures 2 and 3. Localized LCH was present in eight of 19 patients, affecting bony sites without soft tissue involvement in four patients and lymph nodes or the lung exclusively in two patients each.

Clinical Course

Localized disease took a benign course with remission in the eight patients with bone or lymph node involvement and spontaneous transition to inactive disease in isolated pulmonary LCH. Active LCH passed to inactivity after 6–24 months (median 6 months) of a symptomatic course, and remained in the inactive stage during 17–192 months (median 57 months) of further follow-up. Five patients had no evidence of disease, one patient remained stable and asymptomatic, and two patients were stable but symptomatic with the inactive stage of LCH. In patients with multifocal LCH, the course was more aggressive. There was persistent disease activity despite different treatment modalities in seven patients during 18–144 months (median 41) and one patient died after 18 months of follow-up. Disease passed into a stable symptomatic or asymptomatic stage after 6–120 months (median 42 months) in four patients. Complete remission was observed in none of our patients with multifocal LCH.

Some features of LCH were related to the organ system

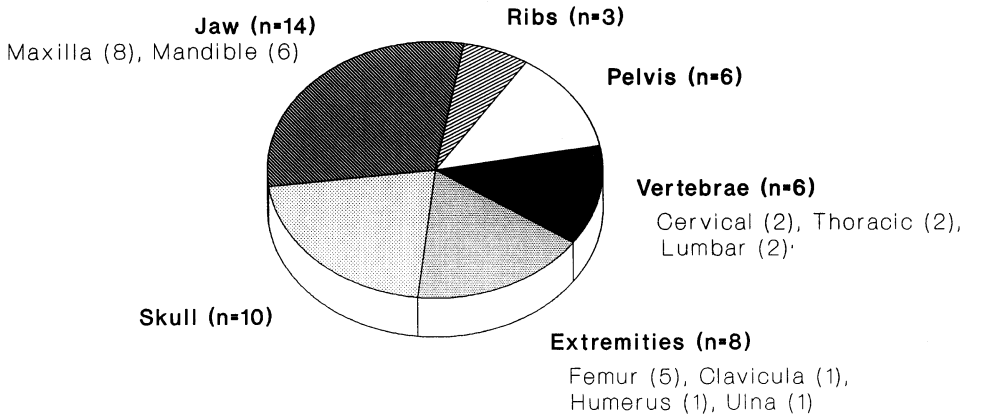

Fig. 3. Location of the bone lesions (n = 47) in 16 patients in the present series.

involved. Twelve of 27 isolated bone lesions were asymptomatic and seven remained unchanged during follow-up (range 8–30 months). A lasting complete or partial local remission was achieved with primary treatment in 12 of 16 symptomatic isolated bone lesions. Five local recurrences occurred within 5–24 months, but responded to another treatment. The course of isolated bone lesions was equally benign in localized and multifocal LCH. Bone lesions with adjacent soft tissue involvement (n = 20) differed distinctly. Lesions occurred within the orodental and otomastoidal region (n = 14) or were seen in the axial skeleton (n = 6) and were all symptomatic. Soft tissue infiltration was manifest as orodental ulcers and loss of teeth (six patients), otorrhea and hearing loss from middle ear infiltration (three patients), and painful lesions of the paravertebral or pelvic soft tissues (three patients). Recurrence rate was elevated, with relapses in 17 of 20 lesions within 4–48 months after treatment. Pulmonary LCH caused dyspnea on exertion and a nonproductive cough in six of seven patients. Pneumothorax developed in three patients and a cor pulmonale was manifest in two with chronic progressive disease. The two patients with localized pulmonary LCH developed stable inactive disease. Vital capacity stabilized above 50% of predicted value and disease remained localized. In comparison, patients with multifocal LCH and lung involvement suffered chronic progression of the disease with increasing disturbances in their functional capacity. Infiltration of the pituitary gland was evident in all patients with diabetes insipidus, and panhypopituitarism with amenorrhea, hypothyroidism, and signs of adrenal gland failure was apparent twice. Further lesions involving the central nervous system were not found. Lymphoreticular organ involvement was seen as a benign localized lymph node infiltration with cure by local treatment in two patients or in relation to progressive multifocal disease in those three patients with involvement of the liver or bone marrow. These patients had marked constitutional symptoms and an elevated sedimentation rate. One disease-related death in a patient with bone marrow involvement was due to a transition to rapidly progressive monomyelocytic leukemia 18 months after the diagnosis of LCH. There has been no chemotherapy prior to the leukemia, but local irradiation of the affected axial skeleton was performed 11 months before death.

Treatment

Treatment regimes were not uniform but, at the discretion of the attending physicians, included a wide range of therapeutic modalities. The effect of different treatment modalities on organ systems involved by LCH is summarized in Table I. Radiotherapy (mean 22, range 18–30 Gray [Gy] was applied to three patients with bone lesions limited to osseous structures (n = 5). Transitory response was achieved in all, followed by local recurrences in three. One bone lesion recurred twice at the same location in spite of irradiation with 24 and 18 Gy (interval 18 months). In four patients with bone/soft tissue lesions (n = 8), irradiation (mean 24, range 20–27 Gy) achieved an initial response at all eight sites. However, only three lesions had long-lasting remission and five lesions recurred. Disease extension to other sites was not prevented by radiotherapy and further manifestations subsequently appeared in six patients. In pituitary gland involvement with panhypopituitarism, radiotherapy failed to bring an improvement.

Five patients with isolated bone lesions (n = 7) treated surgically (curettage or resection) showed satisfactory results with remission in five and a recurrence after transitory response in two cases. Surgical treatment of 14 bone/soft tissue lesions in six patients achieved three remissions, but 11 lesions recurred. Disease extension to other sites occurred in two patients following surgical excision of isolated bone lesions and in five patients with surgically treated bone/soft tissue lesions.

Postoperative irradiation (mean 25, range 20–30 Gy) in combination with surgery in three patients with an isolated bone lesion (n = 3) and in one patient with limited lymph node involvement achieved complete remission. The combined treatment of irradiation (mean 25,

TABLE I. Effect of Various Treatment Modalities on LCH Involving Different Organ Systems

Organ system	No. patients	No. lesions	Remission[a] No. lesions	Recurrence No. lesions	No response No. lesions	Extension[b] No. patients
Radiotherapy						
Bone[c]	3	5	2	3		3
Bone/soft tissue[d]	4	8	3	5		3
Surgery						
Bone	5	7	5	2		4
Bone/soft tissue	6	14	3	11		5
Surgery/postoperative						
Bone[e]	3	3	3			
Radiotherapy						
Lymph node[f]	2	2	2			
Bone/soft tissue[g]	6	7	3	4		5
Systemic treatment[h]						
Bone	2	2	1	1		1
Bone/soft tissue	2	4	1	1	2	1
Lung	5		1		4	3

[a]Partial and complete remission.
[b]Disease extension to other sites.
[c]Mean dose 22 (range 18–30) Gy.
[d]Mean dose 24 (20–27) Gy.
[e]Mean dose 25 (range 20–30) Gy.
[f]Mean dose 23 (range 20–26) Gy.
[g]Mean dose 25 (range 16–45) Gy.
[h]Glucocorticoids, cytotoxic drugs.

range 16–45 Gy) and surgery brought less convincing results in six patients with bone/soft tissue lesions (n = 7). There were three remissions, but four local recurrences. In this group, five patients experienced disease extension to other sites.

Systemic treatment (glucocorticoids, cytotoxic drugs) administered to two patients with bone lesions (n = 2) achieved one partial and one complete remission. However, 3 years after complete local remission, one patient developed multiorgan involvement. Two patients with bone/soft tissue lesions (n = 4) treated with glucocorticoids and cytotoxic drugs showed no response twice, one partial remission, and one recurrence after initial response. Further symptomatic manifestations of disease evolved in one of these two patients. Systemic treatment with glucocorticoids and/or cytotoxic drugs was administered to five patients with pulmonary LCH. A convincing benefit of systemic treatment could not be demonstrated in these patients (Table I).

DISCUSSION

LCH belongs to a spectrum of histiocytic disorders which have in common their involvement of the mononuclear-phagocyte system and LC proliferation. In this series, diagnosis depended on the histopathologic evidence of LC as a distinctive component of the lesion and the immunohistochemical expression of S-100 protein. Conditioned by the retrospective observation with reevaluation of former biopsy samples, stains for ATPase, alpha-D-mannosidase, or binding of peanut lectin and electron microscopy were not done, but at least one of these features are demanded by the Histiocyte Society for definitive instead of presumptive diagnosis [3]. However, various biopsies of involved tissues and proof of S-100 protein are clearly indicative of the diagnosis of LCH.

In this series of adult patients, disease was found most often in the skeleton or lung similar to other observations [7,9,20]. In childhood, bone lesions are described as a common finding, but lymphoreticular organ involvement is found more than twice as frequently as compared to this series [5,6,18,20]. Although overall survival seems to be better in adults with lymphoreticular disease, liver and bone marrow involvement was associated with an unfavorable course of disease and one patient with bone marrow infiltration died of acute leukemia. Our cases of pulmonary LCH are too small to compare incidence and prognosis to the childhood form.

A typical features of LCH in adulthood was the preferential involvement of the axial skeleton and skull [9,21]. The decisively different prognosis of isolated bone lesions compared to bone lesions with adjacent soft tissue infiltration is a finding that has so far not been sufficiently recognized. Isolated bone lesions, single or multifocal, had a benign course in contrast to bone lesions associated with an adjacent soft tissue infiltration. The involvement of surrounding soft tissues was associated with more symptoms, poorer therapeutic response, and frequent recurrences following irradiation or surgery, particularly in

the orodental and otomastoid region [22]. The reason for this more unpredictable treatment-resistant course in bone/soft tissue lesions is unsettled, the size of single lesions as well as histopathology not differing from isolated bone lesions. Another frequent site of LCH in adults is the lung. Even though only a few patients were analyzed, we found less functional deterioration and better overall prognosis in the localized than the multifocal form of LCH. In general, most patients showed a spontaneous transition to inactive stable LCH in accordance with Friedman et al.'s series [10]. With pituitary gland involvement, diabetes insipidus was manifest without exception. Other endocrine symptoms appeared sporadically and exclusively in combination with diabetes insipidus. The frequency of isolated involvement of the pituitary gland region is unknown, but must be suspected in patients with diabetes insipidus [7,11,23]. Lymph node involvement seems to differ from the more aggressive multifocal form of LCH with liver or bone marrow infiltration. However, the number of patients is too small to allow reliable conclusions. One patient with multifocal LCH, bone marrow disease proved fatal when it progressed to acute monomyelocytic leukemia. LCH is rarely associated with malignant hemopoietic neoplasms, but an association with acute leukemia or malignant lymphoma has been reported [2,6,24]. Because LC are believed to originate from medullary stem cells of the mononuclear phagocyte system, it can be assumed that there is a defect involving monoblasts initially differentiating into abnormal histiocytes with the capacity for proliferation and subsequent transformation into malignant monoblasts. The evolution of acute leukemia 18 months following the diagnosis of histologically verified LCH supports the theory that a mononuclear phagocyte system lineage disorder at the monoblast level may be responsible for both disease entities. A chemotherapy-associated secondary neoplasm was excluded in this case.

The effective treatment for LCH remains controversial at present [25–29]. Since ours was a retrospective study and patients had not been treated in a uniform fashion, we cannot comment on whether specific therapeutic modalities are warranted or superior to previously reported regimens in children. In our series, best results were obtained with a combination of surgery and postoperative irradiation in localized LCH and isolated bone lesions of multifocal disease. However, it is the nature of the lesion (bone, lymph node, bone/soft tissue) that determines whether remissions are lasting or not. Higher initial doses of radiation (35–40 Gy) did not prevent recurrences in bone compared to lower doses (18–20 Gy). Limited experience with patients with nonosseous involvement does not allow a critical appraisal of the effectiveness of systemic treatment in visceral involvement. In the literature, vinblastine, vincristine, prednisone, and cyclophosphamide, either alone or in combination, are mentioned in the treatment of disseminated disease. Nevertheless, no modality has clearly shown convincing results, with remission rates varying between 21 and 65% [4,28–30]. In primary pulmonary LCH, one prospective study showed an advantage of glucocorticoids given in early stages of the disease [31]. Spontaneous remissions and transition into inactive disease should restrict systemic treatment. In advanced stages with severe functional impairment, lung transplantation may be considered, although it is unknown whether LCH will recur.

Considerable morbidity and the tendency for dissemination would justify controlled trials of new therapeutic regimes. Cyclosporine and alpha-interferon may lead to a restoration of the immunologic changes and clinical response in some patients with LCH [32–35]. The recent case reports of successful alpha-interferon treatment in view of the mentioned pathogenesis of immune dysregulation are of particular interest. Another promising approach is the use of 2-chlorodesoxyadenosine (cladribine), which reportedly led to complete remission in three patients with long-standing disease [36].

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